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Resource utilization and costs in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme

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Aims More treatments are needed to improve clinical outcomes in chronic heart failure (HF). It is, however, important that treatments for a condition as common as HF are affordable. We have carried out a prospective economic analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme.
Methods and results Patients with NYHA class II–IV HF and LVEF $\leq$0.40 were randomized to CHARM-Alternative if intolerant of an ACE-inhibitor or to CHARM-Added if taking an ACE-inhibitor. Patients with a LVEF $>$0.40 were randomized in CHARM-Preserved. Each trial compared the effect of candesartan to placebo on the primary outcome of cardiovascular death or HF hospitalization. Detailed information was prospectively collected on hospital admissions, procedures/operations and drugs. A cost–consequence analysis was performed for France, Germany and the UK for CHARM-Overall and a cost-effectiveness analysis for the low LVEF trials. The cost of candesartan was substantially offset by a reduction in hospital admissions, especially for HF. In the cost–consequence analysis, candesartan was cost-saving in most scenarios for CHARM-Alternative and Added but the marginal annual net cost per patient was upto €372 per year in CHARM-Preserved, in which candesartan did not reduce the primary outcome significantly. In the cost-effectiveness analysis of patients with a LVEF $\leq$ 0.40, candesartan was cost-saving in some scenarios and in the others the maximum cost per life year gained was €3881.
Conclusion Candesartan improves functional class, reduces the risk of hospital admission, and increases survival in patients with a HF and a LVEF $\leq$0.40 at an acceptable cost.

Introduction

Despite the availability of several effective treatments,[1,2] patients with chronic heart failure (HF) continue to experience marked functional limitation because of symptoms, reduction in quality of life, frequent admission to hospital, and greatly shortened life-expectancy.[3–7] Consequently, HF continues to be a major public health problem, for which new treatments are needed.[8] For a condition as prevalent as HF, the cost of any new treatment (and whether it is justified) is, inevitably questioned.[9–14] We have recently shown that the angiotensin II type 1 receptor blocker (ARB) candesartan reduces symptomatic limitation and decreases the risk of hospital admission for worsening HF and deaths due to cardiovascular causes, when added to conventional treatment in a broad spectrum of patients with symptomatic HF randomized in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme.[15–21] An economic evaluation of this programme was pre-specified and data on resource use were collected prospectively. Here we describe within-trial cost–consequence and cost-effectiveness analyses of CHARM.[15]

Methods

The CHARM programme

The design, baseline findings, and primary results of the CHARM programme have been reported in detail.[15–21] Briefly, the CHARM programme consisted of three independent but related trials in which patients with NYHA class II–IV HF were randomized to

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placebo or candesartan (target dose 32 mg once daily). In CHARM-Added, patients in NYHA Class II had to have had a hospital admission for a cardiac reason in the previous 6 months (this had the effect of increasing the proportion of NYHA class III/IV patients in CHARM-Added). Patients were enrolled into the individual CHARM trials according to left ventricular (LV) ejection fraction (EF) (LVEF) and baseline treatment with an ACE-inhibitor. Patients with an LVEF $\leq$0.40 and intolerant of an ACE-inhibitor, were enrolled in CHARM-Alternative,[17] whereas patients with an LVEF $\leq$0.40 and taking an ACE-inhibitor were enrolled in CHARM-Added.[18] Patients with an LVEF $>$0.40 were randomized into CHARM-Preserved.[19] The CHARM programme was completed, as planned, 2 years after the last patient was randomized. Because the rate of recruitment varied between the CHARM trials, overall follow-up ranged from a median of 41 [interquartile (IQR) range 35–44] months in CHARM-Added, to 37 (34–41) months in CHARM-Preserved, 34 (27–41) months in CHARM-Alternative, and 38 (32–42) months in the overall CHARM programme.[17–20]

Economic analysis of CHARM

These analyses were based on the comparison of placebo, i.e. conventional treatment for HF (combination of a diuretic, digoxin, ACE-inhibitor, beta-blocker, and spironolactone, as indicated and tolerated) to candesartan added to conventional treatment. We examined the effect of adding candesartan in all 7599 patients randomized in 26 countries. For the purposes of the economic analysis, however, all patients were considered to have been managed in France, Germany, or the UK. Our analysis takes the perspective of a third party payer in France and Germany and the National Health Service (NHS) in the UK. Information was collected prospectively on drug treatment, patients admitted to hospital (proportion admitted, number of admissions per patient, number of hospital days per patient), admissions for cardiovascular reasons (number, duration, ward type), and procedures/operations as described below. These data were used to determine the additional direct costs incurred, and potential savings made with candesartan. Indirect costs such as loss of productivity and earnings due to inability to work were not considered. The analysis period was that of the trial concerned and the programme overall; no future projections were made.

Effectiveness measures

As described in detail elsewhere, the primary clinical outcome in the component trials of the CHARM programme was the composite of cardiovascular death or hospital admission for worsening HF.[15–21] The candesartan to placebo hazard ratio for this outcome in CHARM-Alternative was 0.77 (95% CI 0.67–0.89, $P = 0.0004$),[17] in CHARM-Added 0.85 (0.75–0.96, $P = 0.011$),[18] in CHARM-Preserved 0.89 (0.77–1.03, $P = 0.118$),[19] and in the overall CHARM programme 0.84 (0.77–0.91, $P < 0.0001$).[20]

All-cause mortality was the pre-specified primary endpoint of the overall CHARM programme and of the two reduced LVEF trials combined (CHARM-Alternative and Added).[15] The candesartan to placebo hazard ratio for this outcome in the overall CHARM programme was 0.91 (0.83–1.00,[20] $P = 0.055$) and in the reduced LVEF trials 0.88 (0.79–0.98, $P = 0.018$).[21]

Resource use

Hospital admissions. For cardiovascular admissions, investigators were asked to specify the type of ward (intensive/coronary care unit, cardiology, general internal medicine) patients were admitted to and the number of days spent in each type of ward.

For non-cardiovascular admissions only, length of stay (and not ward type) was collected. For these admissions, we assumed that 10% of time was spent in intensive care and 90% on an internal medicine ward.

Procedures. Investigators were asked to provide information on cardiovascular procedures and operations (a checklist menu was provided). Non-cardiovascular procedures were not recorded and were assumed to be equal in the two groups.

Drug treatment. Investigators classified medication as cardiovascular or non-cardiovascular. We assumed that non-cardiovascular medication did not differ between treatment groups (and was not, therefore, used in this analysis). 'Cardiovascular' medication included digitalis glycosides, diuretics, beta-blockers, calcium channel blockers, other vasodilators, anti-arrhythmic drugs, ACE-inhibitors, ARBs, and other cardiovascular drugs such as lipid-lowering agents and anticoagulants.

Estimation of costs

Hospital admissions

Two approaches were used, as described previously (*Table 1*).[22]

- Diagnosis-related group (DRG) costs were obtained from government sources in France, Germany, and the UK.[23–28]
- *Per diem* (hospital bed-day) costs were also obtained from official sources in these countries.[23–28] In this analysis actual recorded days in hospital were multiplied by the daily unit costs of hospital care.

Drug treatment

Drug costs were obtained from standard tariffs for the financial year 2003–04 (Vidal, France; Rote Liste, Germany; British National Formulary, UK).[29–32] Daily dose was multiplied by the cost per dose to calculate the daily cost of treatment. Where available, the costs of generic drugs were used. Dispensing fees were included in the public price of candesartan. We added costs to account for the initiation and up-titration of candesartan, namely four extra GP visits and four checks of blood biochemistry, as previously described.[22]

Cardiovascular procedures

The DRG costs of cardiovascular procedures and operations were obtained from local government sources.[23–29] Because little reliable and comparable public information is available for the *per diem* costs of cardiovascular procedures, DRG costs were used as proxies in the *per diem* analysis.

All costs were converted to 2003 values using the local price index with the exception of drug prices which are for 2003–04. Costs are presented in the local currency (£ and €) where £1 = 1.79 US$ and 1€ = 1.20 US$. The recommended discount rate of 3% was used.[33]

The costs used in this analysis are summarized in *Table 1*.

Economic analyses performed

Two types of economic analysis were performed:

- A cost–consequence analysis was performed for each component trial and for the overall CHARM programme. In this, we used the primary outcome of the component trials as the measure of effectiveness i.e. we calculated the cost per patient treated to postpone or prevent one patient experiencing a cardiovascular death or hospital admission for worsening HF within the trial.[34]
- Incremental cost-effectiveness ratios [cost per life year gained (LYG)] were calculated for the reduced LVEF trials as, in these two trials combined, there was a significant increase in survival with candesartan. This analysis was not performed for CHARM-Preserved as there was no reduction in cardiovascular or all cause mortality in that trial with candesartan.

Sensitivity analyses

The following sensitivity analyses were conducted: (i) we increased the length of non-cardiovascular hospital stay by 30% to model for the potential additional cost of certain adverse effects (e.g. renal

Table 1 Unit costs used in the economic analysis of CHARM

Event	DRG costs		
	France 2003	Germany 2003	UK 2003
Hospitalizations			
Worsening HF	4 174	2 951	2 173
Myocardial infarction	4 579	4 140	2 045
Unstable angina	2 526	1 944	1 150
Stroke			
Haemorrhagic	4 394	3 855	2 588
Ischaemic/Unknown/Other	4 394	3 855	3 408
Transient ischaemic attack	2 520	2 445	1 444
Cardiogenic shock	2 779	2 398	1 711
Atrial tachyarrhythmia	2 675	1 876	1 411
Ventricular arrhythmia	2 804	4 615	1 411
Pulmonary embolism	4 969	3 929	2 115
Other cardiovascular event	3 257	1 770	1 368
Cancer (neoplasm)	4 826	3 288	1 960
Other non-cardiovascular event	4 560	2 525	1 235
Cardiovascular procedures			
Cardiac catheterizations including angiography	3 199	1 517	1 668
Coronary artery bypass grafting (CABG)	15 289	11 363	9 491
Percutaneous transluminal coronary intervention (PTCA) with stent	6 166	3 209	5 818
PTCA without stent	2 981	2 736	3 729
Implantation of cardioverter defibrillator	8 557	23 299	22 955
Implantation of pacemaker	8 581	6 575	5 237
Heart transplantation	73 983	44 864	24 929
Ventricular assist device	7 294	6 903	59 667
Other cardiac surgery for HF	18 303	13 906	9 086
Other cardiovascular procedure/operation	7 426	6 221	3 670
Per diem costs			
Intensive/coronary care unit	1 611	871	1 864
Cardiology ward	682	265	634
General medical ward	520	240	413
Non-cardiovascular admission	629	303	558
Visit general practitioner (GP)	18.60	39.20	29.08
Laboratory test—blood biochemistry	9	1.79	34.3
Candesartan 4 mg	0.62	0.76	0.48
Candesartan 8 mg	0.81	0.88	0.57
Candesartan 16 mg	0.88	1.04	0.73
Candesartan 32 mg	1.15	1.24	0.92

All costs shown in Euro (1€ = $1.20 and £0.67).

impairment) in the candesartan group;[35] (ii) we added costs related to adverse effects not leading to hospital admission e.g. hypotension, renal impairment (those leading to admission are accounted for in base-case scenario), namely one extra general practice visit for each patient requiring dose reduction or treatment discontinuation for an adverse effect or laboratory abnormality; (iii) we varied the length of hospital stay in the *per diem* analysis by ±20% and (iv) for the UK only, we discounted costs by 3.5%, as recommended by the National Institute for Clinical Excellence (NICE).

Statistical methods

Statistical analysis was performed using SAS software (version 8; SAS Institute Inc., Cary, NC, USA). The group mean approach was used to account for early dropouts and missing values, as recommended by Cook *et al*.[36] Bootstrapping was used to test for significance.

Role of the funding source

The CHARM programme was funded by AstraZeneca PLC, who managed the data and whose representatives were involved in the data analysis. The economic analysis was planned by all authors and supervised by J.Mc.M. All data were independently checked by S.S. and J.Mc.M. All authors were involved in interpretation of the data and writing of the manuscript which was prepared independently of the sponsor.

Results

Candesartan was taken by 50.0% of randomized patients ($n = 3803$) for 1050 (SD 318) days on average; the comparable figures for placebo ($n = 3796$) were 50.0% and 1029 (SD 345) days. The mean daily doses of candesartan taken were 16.8 mg in CHARM-Alternative, 16.9 mg in CHARM-Added, and 19.0 mg in CHARM-Preserved (17.7 mg overall), based on all patients in the study over the whole study period.

Clinical effects of candesartan

Hospital admissions—all causes

The rates and number of hospital admissions in the overall CHARM programme and each component trial are shown in

Table 2 and *Figures 1* and *2*. Overall, 63.8% of patients in the placebo (conventional treatment) group were admitted to hospital at least once for any reason. This when compared with 62.4% in the candesartan group [odds ratio (OR) 0.94, 95% CI 0.86–1.03, $P = 0.20$]. The number of admissions per patient hospitalized was 2.96 in the placebo group when compared with 2.82 in the candesartan group ($P = 0.045$). The average length of an individual admission was 8.9 days in the placebo group and 9.0 days in the candesartan group. The average number of days spent in hospital for admitted patients was 26.3 days in the placebo group and 25.2 days in the candesartan group. As a result, treatment with candesartan resulted in fewer hospital admissions (placebo 7182, candesartan 6691 or 1.060 compared with 0.853 admissions per year of follow-up, $P = 0.0001$) and fewer days in hospital (placebo 63 681, candesartan 59 923; *Table 2*, $P =$ ns). The number of days in hospital per patient-year of follow-up was 6.0 in the placebo group and 5.5 in the candesartan group ($P = 0.056$).

Hospital admissions—specific causes

Table 3 and *Figure 2* show the breakdown of patients admitted (and hospital admissions) by specific causes. candesartan reduced both the proportion of patients admitted (−20%) and the number of admissions (−28%) for worsening HF. There was also a trend towards a reduction in atrial tachyarrhythmias. Conversely, there was significant increase in hospitalizations for hypotension (though the absolute numbers for this adverse effect were small i.e. 49 patients in the placebo group and 98 in the candesartan group). These findings were consistent across the component trials except for 'other' cardiovascular admissions, which were fewer in the candesartan group in CHARM-Alternative and CHARM-Added, but numerically greater in the candesartan group in CHARM-Preserved. Examination of these miscellaneous admissions did not reveal an excess in any specific category of event.

Procedures and operations

Cardiovascular procedures are shown in *Table 4*. The number of procedures, other than cardiac catheterization, was small and did not differ between treatment groups.

Cost of adjunctive candesartan treatment: *per diem* analysis

The costs of adding candesartan to conventional treatment (compared with placebo added to conventional treatment), based on the analysis using the *per diem* costs, are shown in *Table 5*.

For France and the UK, the cost of care in the candesartan group was slightly (1–2%) less, even taking into account the cost of candesartan. For Germany, the overall cost of care was slightly higher (4%) in the candesartan group.

The costs of adding candesartan to conventional treatment differed by component trial in the CHARM programme. For all countries, there was a net cost-saving in CHARM-Alternative (0.3–7% reduction in cost) and either no additional cost or a cost-saving in CHARM-Added (0–7% reduction). In CHARM-Preserved, there was a net increase in the daily cost of care for all countries (6–12% increase in cost).

Cost of adjunctive candesartan treatment: DRG analysis

Table 6 shows the results of this analysis in the same way as *Table 5* did for the *per diem* analysis. Although the costs of procedures were higher in France and Germany (and bed-day costs lower) than in the UK, the results of the DRG analysis were very similar to those of the *per diem* analysis. There was a small increase (2–6%) in the net daily cost of care with candesartan for all three countries using the DRG approach. Again, for all the three countries, the estimated net costs with candesartan were generally less in the CHARM-Alternative and -Added trials than in CHARM-Preserved.

Cost—consequence analyses

Translating the clinical findings and the daily costs into annual estimates gives the cost–consequence analysis shown in *Table 7*. Adjunctive treatment with candesartan in CHARM-Alternative and CHARM-Added led to clinical benefits and to either cost-savings or a small additional annual cost, depending on trial and country. The less certain clinical benefit in CHARM-Preserved was obtained at a modest extra annual cost in all the three countries.

Cost-effectiveness analyses

Table 8 summarizes the cost-effectiveness analyses of the two reduced LVEF CHARM trials. These results were calculated using only DRG costs as all scenarios with *per diem* costs were cost-saving in all countries. Using French DRG costs, candesartan was cost-saving in the reduced LVEF trials individually and combined. In Germany, the cost per LYG incremental cost-effectiveness ratio (ICER) was estimated to range from €1427 (CHARM-Added) to €3881(CHARM-Alternative). The results for the UK lay between those of France and Germany, i.e. candesartan was cost-saving in CHARM-Added and the ICER was greatest (but still relatively small) in CHARM-Alternative at €2547 per LYG.

Sensitivity analyses

Increasing the length of stay for non-cardiovascular admissions by 30% increased the cost per day in the candesartan group by 15–20%. As a result, candesartan was no longer cost-saving in any comparison.

Adding one GP visit for an adverse event or laboratory abnormality which led to a reduction in the dose of, or discontinuation of, candesartan resulted in an increase in daily costs of €0.01–0.02.

Varying the length of hospital stay for all admissions by ±20% varied costs in both groups accordingly, but did not change the general conclusions.

Using a 3.5% discount rate did not change the UK results much. Total daily costs were reduced by about €0.04–0.11 in each of the CHARM trials individually and overall, with a similar change in both treatment groups.

Discussion

It is widely accepted that HF accounts for ∼2% of direct health care costs in more developed countries and up to 70% of these are expended on hospital admissions.[9–14] Furthermore, the public health (and economic) burden of HF is widely perceived to be increasing because of the

Table 2 Hospital admissions (any cause) and patients hospitalized (for any cause) in CHARM (totals and means)

	Placebo ($n = 1015$)	Candesartan ($n = 1013$)	Diff (95% CI)	*P*-value
CHARM-Alternative				
All patients				
Patient-years	2 582	2 658		
No. of deaths	296	265		
No. admissions	1 835	1 719		
No. hospital days	16 816	15 079		
Hospital days/admission	9.16	8.77	0.39 (−0.60, 1.38)	0.44
Admissions/patient	1.81	1.70	0.11 (−0.10, 0.32)	0.30
Hospital days/patient	16.57	14.89	1.86 (−1.11, 4.47)	0.24
Hospital days/patient-year	6.51	5.67	0.84 (−0.27, 1.95)	0.13
Patients hospitalized				
No. hospitalized patients	643	610	0.88 (0.73, 1.05)	0.15
Admissions/patient	2.85	2.82	0.04 (−0.25, 0.32)	0.80
Hospital days/patient	26.15	24.72	1.43 (−2.73, 5.60)	0.50
	Placebo ($n = 1272$)	Candesartan ($n = 1276$)	Diff (95% CI)	*P*-value
CHARM-Added				
All patients				
Patient-years	3 721	3 846		
No. of deaths	412	377		
No. admissions	2 799	2 462		
No. hospital days	24 161	21 902		
Hospital days/admission	8.63	8.90	−0.26 (−0.95, 0.43)	0.45
Admissions/patient	2.20	1.93	0.27 (0.07, 0.47)	0.008
Hospital days/patient	18.99	17.16	1.83 (−0.65, 4.31)	0.15
Hospital days/patient-year	6.49	5.70	0.79 (−0.06, 1.64)	0.070
Patients hospitalized				
No. hospitalized patients	858	852	0.97 (0.82,1.14)	0.71
Admissions/patient	3.26	2.89	0.37 (0.13, 0.62)	0.003
Hospital days/patient	28.16	25.71	2.45 (−0.94, 5.85)	0.16
	Placebo ($n = 1509$)	Candesartan ($n = 1514$)	Diff (95% CI)	*P*-value
CHARM-Preserved				
All patients				
Patient-years	4 387	4 434		
No. of deaths	244	237		
No. admissions	2 548	2 510		
No. hospital days	22 705	22 942		
Hospital days/admission	8.91	9.14	−0.23 (−1.02, 0.56)	0.57
Admissions/patient	1.69	1.66	0.03 (−0.13, 0.20)	0.71
Hospital days/patient	15.05	15.15	−0.11 (−2.20, 2.01)	0.92
Hospital days/patient-year	5.18	5.17	0.01 (−0.73, 0.75)	0.98
Hospitalized patients				
No. hospitalized patients.	922	912	0.96 (0.83, 1.12)	0.63
Admissions/patient	2.76	2.75	0.01 (−0.21, 0.23)	0.92
Hospital days/patient	24.63	25.16	−0.53 (−3.71, 2.65)	0.74
	Placebo ($n = 3796$)	Candesartan ($n = 3803$)	Diff (95% CI)	*P*-value
CHARM-Overall				
All patients				
Patient-years	10 690	10 938		
No. of deaths	945	886		
No. admissions	7 182	6 691		
No. hospital days	63 681	59 923		
Hospital days/admission	8.87	8.96	−0.09 (−0.55, 0.38)	0.71
Admissions/patient	1.89	1.76	0.13 (0.02, 0.24)	0.018
Hospital days/patient	16.78	15.76	1.02 (−0.38, 2.42)	0.15
Hospital days/patient-year	5.96	5.48	0.48 (−0.02, 0.98)	0.056
Hospitalized patients				
No. hospitalized patients	2 423	2 374	0.94 (0.86, 1.03)	0.20
Admissions/patient	2.96	2.82	0.15 (0.003, 0.29)	0.045
Hospital days/patient	26.28	25.24	1.04 (−0.99, 3.07)	0.31

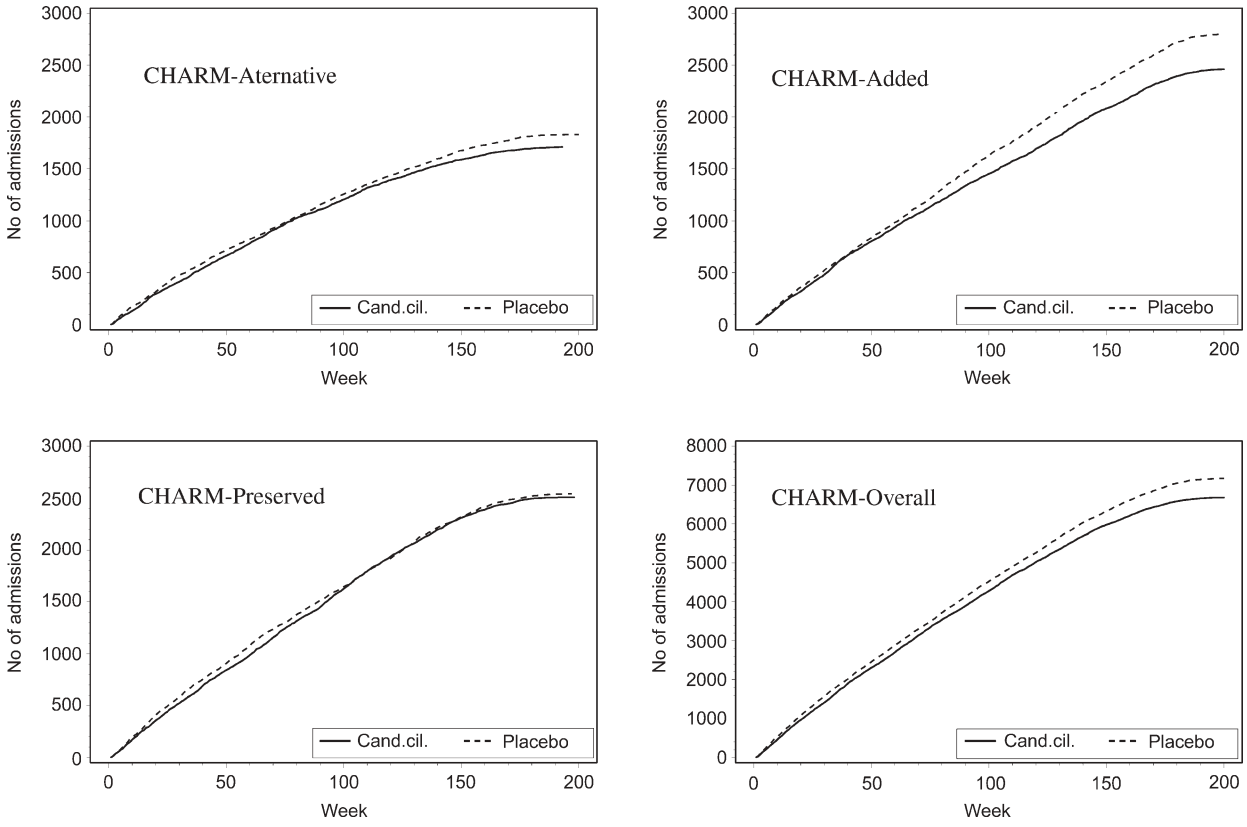

Figure 1 Cumulative number of hospital admissions: CHARM-Alternative (top left), CHARM-Added (top right), CHARM-Preserved (bottom left), CHARM-Overall (bottom right).

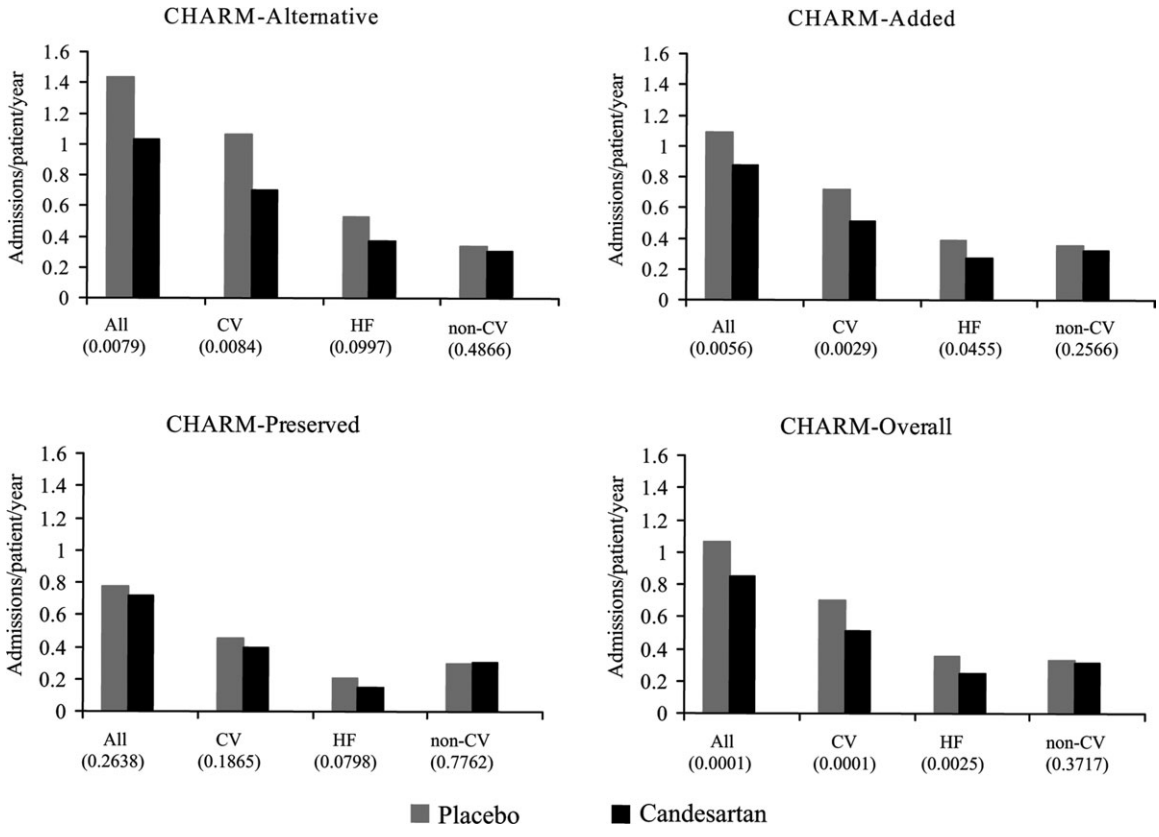

Figure 2 Rates of hospital admission for any cause, all cardiovascular reasons, HF only, and non-cardiovascular reasons. The numbers in parentheses refer to the *P*-values for the comparison of the candesartan and placebo groups.

Table 3 Hospital admissions by cause—number of admissions and number and proportion of patients admitted

	Alternative				Added				Preserved				Overall			
	Placebo ($n = 1015$)		Candesartan ($n = 1013$)		Placebo ($n = 1272$)		Candesartan ($n = 1276$)		Placebo ($n = 1509$)		Candesartan ($n = 1514$)		Placebo ($n = 3796$)		Candesartan ($n = 3803$)	
	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)	Admissions	Patients (%)
Worsening HF	608	291 (28.7)	445	212 (20.9)†	836	382 (30.0)	607	323 (25.3)**	566	279 (18.5)	402	230 (15.2)*	2010	952 (25.1)	1454	765 (20.1)†
Myocardial infarction	51	45 (4.4)	55	48 (4.7)	64	50 (3.9)	38	36 (2.8)	64	61 (4.0)	68	58 (3.8)	179	156 (4.1)	161	142 (3.7)
Unstable angina	109	74 (7.3)	137	94 (9.3)	192	117 (9.2)	145	101 (7.9)	235	145 (9.6)	244	154 (10.2)	536	336 (8.8)	526	349 (9.2)
Stroke	34	32 (3.2)	35	32 (3.2)	38	34 (2.7)	37	34 (2.7)	56	52 (3.4)	52	46 (3.0)	128	118 (3.1)	124	112 (3.0)
TIA	16	15 (1.5)	16	12 (1.2)	10	9 (0.7)	20	19 (1.5)	25	21 (1.4)	21	18 (1.2)	51	45 (1.2)	57	49 (1.3)
Hypotension	14	14 (1.4)	26	20 (2.0)	24	22 (1.7)	60	55 (4.3)†	15	13 (0.9)	25	23 (1.5)	53	49 (1.3)	111	98 (2.6)†
Atrial tachyarrhythmia	44	34 (3.4)	53	34 (3.4)	56	46 (3.6)	61	49 (3.8)	123	86 (5.7)	82	59 (3.9)*	223	166 (4.4)	196	142 (3.7)
Ventricular arrhythmia	55	39 (3.8)	52	45 (4.4)	86	65 (5.1)	68	52 (4.1)	16	14 (0.9)	18	17 (1.1)	157	118 (3.1)	138	114 (3.0)
Pulmonary embolism	9	8 (0.8)	6	6 (0.6)	11	10 (0.8)	6	6 (0.5)	9	9 (0.6)	8	8 (0.5)	29	27 (0.7)	20	20 (0.5)
Other CV event	244	181 (17.8)	225	164 (16.2)	416	254 (20.0)	362	249 (19.5)	368	247 (16.4)	400	280 (18.5)	1028	682 (18.0)	987	693 (18.2)
CV unknown									1	1 (0.0)	1	1 (0.0)	1	1 (0.0)	1	1 (0.0)
Cancer	55	35 (3.4)	42	30 (3.0)	49	36 (2.8)	83	52 (4.1)	84	52 (3.4)	53	40 (2.6)	188	123 (3.2)	178	122 (3.2)
Other non-CV event	596	334 (32.9)	627	350 (34.6)	1017	531 (41.8)	975	525 (41.1)	986	546 (36.2)	1136	589 (38.9)	2599	1411 (37.2)	2738	1464 (38.5)
All	1835	643 (63.4)	1719	610 (60.2)	2799	858 (67.5)	2462	852 (66.8)	2548	922 (61.1)	2510	912 (60.2)	7182	2423 (63.8)	6691	2374 (62.4)

TIA, transient ischaemic attack; CV, cardiovascular.
*$P < 0.05$.
**$P < 0.01$.
†$P < 0.001$ (comparison of proportion of randomized patients).

Table 4 Number of cardiovascular procedures in CHARM

Procedure	Alternative		Added		Preserved		Overall	
	Placebo ($n = 1\,015$)	Candesartan ($n = 1\,013$)	Placebo ($n = 1\,272$)	Candesartan ($n = 1\,276$)	Placebo ($n = 1\,509$)	Candesartan ($n = 1\,514$)	Placebo ($n = 3\,796$)	Candesartan ($n = 3\,803$)
Cardiac catheterization including angiography	160	139	228	172	261	262	649	573
CABG	26	21	22	39	42	46	90	106
PTCA with stent	31	30	55	36	73	78	159	144
PTCA without stent	11	10	19	10	23	15	53	35
Implantation of cardioverter defibrillator	31	30	60	51	9	9	100	90
Implantation of pacemaker	50	49	75	80	54	67	179	196
Heart transplantation	8	7	15	17	0	0	23	24
Ventricular assist device	6	6	3	1	0	1	9	8
Other cardiac surgery for HF	3	2	6	9	10	11	19	22
Other cardiovascular procedure/operation	112	112	213	188	196	192	521	492
Total no. of CV procedures	438	406	696	603	668	681	1802	1690
Total no. of patients with CV procedure (percent of patients)	239 (23.6)	218 (21.5) ($P = 0.27$)	349 (27.4)	320 (25.1) ($P = 0.18$)	350 (23.2)	342 (22.6) ($P = 0.69$)	938 (24.7)	880 (23.1) ($P = 0.11$)

CV, cardiovascular; CABG, coronary artery bypass grafting.

Table 5 Daily per patient cost of treatment in CHARM—*per diem* analysis (standard errors within brackets)

Cost item	Alternative		Added		Preserved		Overall	
	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan
	France (€)							
Hospitalizations	13.26	11.60	13.06	11.44	10.42	10.37	12.03	11.05
Cardiovascular procedures	3.44	3.09	3.87	3.69	2.55	2.61	3.22	3.11
Concomitant medication	1.62	1.56	1.99	1.94	1.60	1.53	1.74	1.68
Study drug	0	0.91	0	0.89	0	0.93	0	0.91
Total	18.33 (3.47)	17.16 (2.23)	18.91 (1.36)	17.96 (1.40)	14.56 (1.40)	15.44 (1.02)	16.98 (1.18)	16.74 (0.86)
	Germany (€)							
Hospitalizations	6.37	5.57	6.28	5.51	5.01	5.00	5.78	5.32
Cardiovascular procedures	2.94	2.68	3.42	3.19	1.89	1.93	2.67	2.55
Concomitant medication	1.76	1.73	1.91	1.89	1.71	1.63	1.79	1.74
Study drug	0	1.05	0	1.02	0	1.07	0	1.05
Total	11.06 (1.80)	11.03 (1.15)	11.61 (0.82)	11.61 (0.77)	8.61 (0.76)	9.63 (0.59)	10.25 (0.63)	10.67 (0.47)
	UK (£)							
Hospitalizations	12.71	11.10	12.47	10.94	9.95	9.89	11.50	10.55
Cardiovascular procedures	2.79	2.56	2.94	2.58	1.61	1.68	2.36	2.21
Concomitant medication	1.45	1.42	1.61	1.59	1.43	1.36	1.49	1.46
Study drug	0	0.81	0	0.78	0	0.81	0	0.79
Total	16.95 (2.68)	15.89 (1.48)	17.02 (0.82)	15.89 (0.81)	12.99 (0.84)	13.74 (0.71)	15.35 (0.84)	15.02 (0.56)

Cardiovascular procedures are based on DRG rates.

Table 6 Daily per patient cost of treatment in CHARM—DRG analysis (standard errors within brackets)

Cost item	Alternative		Added		Preserved		Overall	
	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan
	France (€)							
Hospitalizations	6.33	5.70	6.55	5.55	4.95	4.84	5.84	5.30
Cardiovascular procedures	3.44	3.09	3.87	3.69	2.55	2.61	3.22	3.11
Concomitant medication	1.62	1.56	1.99	1.94	1.60	1.53	1.74	1.68
Study drug	0	0.91	0	0.89	0	0.93	0	0.91
Total	11.39 (1.07)	11.26 (1.76)	12.40 (0.88)	12.07 (0.78)	9.09 (0.68)	9.91 (0.56)	10.80 (0.62)	11.00 (0.45)
	Germany (€)							
Hospitalizations	4.14	3.70	4.20	3.50	3.06	2.92	3.72	3.32
Cardiovascular procedures	2.94	2.68	3.42	3.19	1.89	1.93	2.67	2.55
Concomitant medication	1.76	1.73	1.91	1.89	1.71	1.63	1.79	1.74
Study drug	0	1.05	0	1.02	0	1.07	0	1.05
Total	8.84 (1.41)	9.16 (0.81)	9.53 (0.69)	9.61 (0.55)	6.66 (0.46)	7.55 (0.45)	8.18 (0.48)	8.67 (0.34)
	UK (£)							
Hospitalizations	2.57	2.22	2.55	2.11	1.86	1.73	2.27	1.98
Cardiovascular procedures	2.79	2.56	2.94	2.58	1.61	1.68	2.36	2.21
Concomitant medication	1.45	1.42	1.61	1.59	1.43	1.36	1.49	1.46
Study drug	0	0.81	0	0.78	0	0.81	0	0.79
Total	6.80 (1.53)	7.01 (0.49)	7.09 (0.36)	7.06 (0.25)	4.91 (0.28)	5.58 (0.38)	6.13 (0.44)	6.44 (0.22)

Table 7 Cost–consequence analysis of candesartan compared with placebo in the treatment of HF—clinical benefits and annual per patient saving/cost increase (95% CI)

CHARM Trial	Clinical benefits vs. placebo	DRG costs			*Per diem* costs		
		France	Germany	UK	France	Germany	UK
Alternative	CV deaths (−15%)	Savings	Net increase	Net increase	Savings	Savings	Savings
	HF admission (−32%)	(€49 ± 1475/year)	(€117 ± 1164/year)	(€76 ± 1150/year)	(€428 ± 2952/year)	(€12 ± 1529/year)	(€391 ± 2192/year)
Added	CV deaths (−16%)	Savings	Net increase	Savings	Savings	Savings	Savings
	HF admission (−17%)	(€120 ± 841/year)	(€29 ± 631/year)	(€15 ± 314/year)	(€346 ± 1397/year)	(€0.2 ± 805/year)	(€419 ± 825/year)
Preserved	CV deaths (−1%), ns	Net increase	Net increase	Net increase	Net increase	Net increase	Net increase
	HF admission (−15%)	(€299 ± 630/year)	(€327 ± 460/year)	(€246 ± 337/year)	(€321 ± 1240/year)	(€372 ± 689/year)	(€276 ± 787/year)
Overall	CV deaths (−12%)	Net increase	Net increase	Net increase	Savings	Net increase	Savings
	HF admission (−21%)	(€73 ± 548/year)	(€176 ± 421/year)	(€116 ± 352/year)	(€88 ± 1045/year)	(€153 ± 563/year)	(€122 ± 749/year)

ageing of populations in developed countries (elderly individuals having a greater prevalence of cardiovascular disease) and improving survival from conditions increasing the risk of future HF (e.g. myocardial infarction).[8,11] Consequently, it is hoped that new treatments for HF will not only improve symptoms and reduce mortality, but also decrease hospital admissions and, in doing so, cut costs. Given the relationship between the cost of hospitalization and the overall cost of HF to society, any treatment that substantially reduces hospital admission rates is likely to be cost-effective.[10,14] That is precisely what we found in this pre-planned economic analysis of CHARM. A substantial reduction in the proportion of patients admitted with worsening HF (and an even more marked reduction in the number of such admissions), without any increase in length of stay, contributed to a reduction in the rate of admission (and hospital bed days) for any reason, though this overall reduction was more modest. This is because the full impact of the reduction in admissions for worsening HF was attenuated by increased survival in the candesartan-treated patients (who, therefore, spent more time at risk of hospital admission for other reasons). Nevertheless, the cost-savings accruing from even this modest reduction in the rate of hospital admission for any cause largely offset the cost of candesartan. Though the final result varied slightly between the countries studied and according to the method of analysis (*per diem* compared with DRG), candesartan was, essentially, cost-neutral in the overall-CHARM programme (though clinical effectiveness was not proven in one component trial, CHARM Preserved). There was, however, heterogeneity between the component trials in the programme. Although candesartan treatment was associated with either a small reduction or increase in the net overall cost of care in CHARM-Alternative and CHARM-Added, depending on the analysis, in CHARM-Preserved (in which candesartan treatment did not reduce the primary endpoint significantly) there was a consistent and modest increase in the net cost of care. There appear to be two reasons for this. Though the proportional reduction in the rate and number of admissions for worsening HF was similar in all three CHARM trials, the absolute number of admissions prevented was smaller, relative to the number of patients treated, in CHARM-Preserved (i.e. the rate of admission for worsening HF was lower in CHARM-Preserved, *Figure 2*). Consequently, the cost-offset was less in CHARM-Preserved than in the other two trials. A second explanation was the increased number of 'other' cardiovascular admissions in the candesartan group in CHARM-Preserved (a reduction, rather than excess, of these admissions was observed in the other CHARM trials). A similar increase was observed with cardiovascular procedures in CHARM-Preserved. No clear pattern could be discerned in either excess suggesting that both increases may have been a chance finding. That the overall net cost of treatment in CHARM-Added was comparable with that obtained in CHARM-Alternative is notable, given that candesartan was added to full conventional treatment, including an ACE-inhibitor, in the former trial. It is also notable that the essentially cost-neutral outcome of these analyses of CHARM was obtained despite adding the cost of extra clinic visits and biochemical tests to reflect the extra costs related to initiating, up-titrating the dose, and monitoring the effects of candesartan.

Table 8 Cost effectiveness of candesartan in the CHARM reduced LVEF trials (based on DRG costs)

CHARM Trial	LYG (95% CI)[a]	Cost per LYG (95% CI)		
		France	Germany	UK
Alternative	0.078 (0.003–0.15)	Dominant	€3881 (−17 728; 1 105 920)	€2547 (−18 171; 1 059 150)
Added	0.061 (−0.002–0.12)	Dominant	€1427 (−14 479; −984 755)	Dominant
Reduced LVEF pooled	0.068 (0.02–0.12)	Dominant	€2997 (−19 183; 121 500)	€1348 (−16 225; 106 600)

Dominant means a cost per LYG could not be calculated because costs were lower in the candesartan than in the placebo group.
[a]Within trial and discounted.

Our findings on the cost–consequences of using candesartan are broadly in keeping with economic analyses of other effective treatments for HF though difficult to compare directly.[22,37–39] No other placebo-controlled study included such a broad spectrum of patients, had within-trial data for such a long period of follow-up (with the exception of the ACE-inhibitor enalapril in the treatment arm of the studies of LV dysfunction in the case of the latter[36]), or added the test drug to such extensive background treatment. Nevertheless, a consistent message from these prior economic analyses and ours is that reduction in hospital admission offsets the cost of treatment. Remarkably, the cost-offset has been sufficient with all treatments examined, to date, to be cost-saving or more or less cost-neutral. This is despite each new drug being used as an additional treatment and against a trend of falling lengths of hospital stay.

These economic results, coupled with the clinical findings of the CHARM programme, have clear implications for the management of patients with HF.[17–21,40] Not only does candesartan improve all important clinical outcomes in HF but also offers these benefits at little or no additional cost to the health care system; indeed, its use in patients with HF and reduced LV systolic function may lead to an actual reduction in the direct costs of health care. This is an important finding for health-care providers and society more generally, because there is no trade-off between the interest of the individual patient (and it seems unlikely that many patients would prefer the outcomes expected without candesartan) and the greater population served by the health-care system.

As with any analysis of this type there were limitations. By using the full unit cost of candesartan, our analyses have reduced the cost-effectiveness of this treatment for countries such as France where the patient or a private insurer pays 35% of the cost of treatment. We did not take account of indirect costs, such as loss of productivity due to inability to work; this, however, was unlikely to be a major problem because 54% of patients were beyond retirement age at the time of randomization. Pension payments in those who survived were not taken account of and there were more survivors in the candesartan group. We did not consider the cost related to death out of hospital, though there were more of these in the placebo group, this was a conservative approach. We did not incorporate quality of life information. We had less detailed and complete information on non-cardiovascular procedures and drugs. However, the main driver of costs is hospital admission and we did have information on these and tried to account for lack of information on the former in our sensitivity analyses. As with all economic analyses based on clinical trials of limited duration, there is concern that costs may only be postponed and that there may be 'catch-up' over the whole life-time of a patient. We believe that this is unlikely given the relatively long-duration of follow-up of CHARM (37.7 months) compared with the average life-expectancy of patients with HF. Another question about economic analyses is how far they can be generalized, geographically. We chose to focus on France, Germany, and the UK because robust national costs are available from government sources in these countries. We found very similar net consequences in each country and this finding and prior analyses suggest that broadly similar conclusions can be anticipated in other countries, given that in all countries, the cost of HF is mainly driven by hospital admissions. Clearly, however, a greater unit cost of candesartan, shorter (or otherwise less expensive) hospital stays or, especially, both, would make the cost outcome less favourable. Finally, we carried out a cost–consequence analysis of CHARM-Preserved even though the pre-specified primary outcome was not reduced significantly.

In summary, when added to currently recommended treatment, candesartan improves functional limitation due to symptoms,[40] reduces hospital admissions for worsening HF[17–20] and increases survival in patients with HF and a low LVEF[20,21] and does this at little or no extra direct cost to the health-care system. candesartan is, therefore, a clinically and economically attractive adjunctive treatment for those patients, representing a 'win-win' scenario for both the individual patient and health-care providers.

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